Guideline for
Conducting Risk based Post Market Surveillance plan

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1. Introduction

Post-marketing monitoring is one of the important monitoring activities that occur after the market approval of the drug. Due to the adoption by the Egyptian Drug Authority of a new approach to reduce the number of batches subject to analysis, both for pharmaceutical and biological products, for biological there has been a lot release policy for categorizing the biological and according to specific factors they have been classified and match the risk of these product to the frequency of testing , as well as the vitality of the importance of trading products, monitoring after shopping has become one of the important activities for quality control of those products through Developing a risk-based plan depending in the first place on the extent to which the products are subject to analysis before trading.

The post-marketing control process is not limited to regular inspections of manufacturers, distribution companies, warehouses, pharmacies, and risk-based of products for analysis, but extends to following up on any reports on the safety of products and reporting them to pharmacovigilance; In addition to monitoring the promotion of poor-quality products; dealing with market complaints; Remove and dispose of incompatible products.

EDA ensuring that a post-marketing surveillance program is supported by appropriate legal frameworks, staffed with a qualified and proficient regulatory workforce, and financed through regular and adequate national budget appropriations, helps ensure continued operational sustainability.
Regular strategic planning efforts with key stakeholders are also critical in ensuring that approaches, assumptions, and priorities for the post- marketing surveillance program remain relevant over time.

2. Purpose

The objectives of the post-marketing sampling and testing programs are derived from the legal requirements:

1- Monitoring the safety, quality and efficacy of biological available in the market in different regions/regions at different levels of distribution/supply chain with a view to assessing patients' exposure to poor quality biological and suggesting appropriate actions
2- To identify potential causes of low quality of certain products to which patients are exposed.
3- To test the quality of biological in order to identify non-compliant manufacturers with quality standards and in adopting regulatory measures.
4- To detect and report any counterfeit products penetrating the market and what the health impact may be on patients.
5- To identify medicinal products SF that reached consumers and evaluated pharmacovigilance reports by healthcare professionals and patients.
6- To raise awareness of the importance of reporting an unusual deficiency in the effectiveness of medicinal products
7- To improve and enhance safety measures, which include statistical analysis of adverse drug reactions (ADRs) have also been reported by healthcare institutions and patients, thus revealing signs of adverse drug interactions that may require further investigation.

EDA is considering what is achieved from these goals is a factor to evaluate the provisions of control over the drug market and the strengths and weaknesses of the system are identified and the ability to continuously develop. Adoption of a risk-based approach to market surveillance would allow the NCL to optimize the use of their limited resources on those areas considered most likely to pose a risk of quality defects.

3. Scope

This guide will be applied to biological except vaccines, antisera, antitoxins & plasma derived medicinal products. Covering all points of the supply chain, whether distribution companies, warehouses or pharmacies, whether public or private, and given the presence of other parties that have entered the supply chain, such as vaccination centers or even vaccination campaigns, this has been taken into account in the development of the risk-based plan.

Criteria for exclusion based on risk:

1- These products are independently tested by EDA and released for all batches.
2- Vaccines in Egypt are categorized into :
   - National immunization vaccines (EPI and COVAC) where all these vaccines undergone full testing of all batches during lot release, in addition being trade in governmental hospitals, health care units or vaccination centers where tight supply chain is provided and GSDP and cold chain is provided
   - Non-National immunization vaccines (private market) since these are imported from registered authority with no history of non-compliance in testing or as SF product in market.
3- Antisera & Antitoxins are not marketed but are for governmental use only.
4- Albumin & Anti-RH are restricted for hospital use.

Based on risk these products may be targeted for PMS surveillance at any time.

4. Methodology

- This Post marketing surveillance risk-base (PMS-RB) plan will be divided along the 4 quarters of the year; every quarter will target different groups of products with different risk category.
- Four groups of targeted products categories [A, B, C, D] will be designed to ensure effective control of medicinal products based on the risk-based approaches.
- The Product *Category A* that was chosen to start with during the first quarter, and then will be joined by other *Groups B, C and D* which will be

formulated and put into the plan by end of respectively for each quarter.

5. Preparing to Implement Post-Marketing Surveillance Programs

The sampling and testing plan must ensure that sampling is unbiased, and the data produced are meaningful and accurate in order to be used for decision-making.
Sampling and testing activities conducted at least once per year. The initial planning under the NRA is coordinated with all sharing stakeholders.

The NRA establishes clear procedures and guidelines on how to execute all steps of sampling and testing, including clear definition of roles and responsibilities of all parties involved.

The NRA leads sampling, testing activity and finalizes the plan of each program. The NRA inspectors carry out sampling according to an established and approved plan. The Official NCL carry out QC tests according to regulations and guidelines (official verified/validated test methods in product dossiers, or pharmacopeia methods). Data are analyzed and reported to the PMS department which is responsible for sharing with all relevant stakeholders. The NRA carries out follow-up actions.

Substitution criteria should be developed to address the following scenarios when they occur:

- The selected sampling outlet is closed, or the governorate does not have a branch of authorized distribution companies, then the outlet can be substituted by the nearest health institution found in the same area.
- The biological being sampled is not found in the selected sampling outlet the trial of sampling will be repeated from the same governorate.
- The biological is not available, then exchange the product with another available to replace it in the plan from another governorate.
- The biological in the outlet has less than six month's shelf life.

The supply of biological is limited, and the biological is necessary for life of the patient, then the product would be changed in that site.

- The minimum quantity of biological needed is not available during sampling.

6. Designing of plan

Develop a PMS risk-based plan for the biological should be matching with the lot release plan which is implemented according to the set timetable.

Risk-based plans provide all technical information about the tests to be used, product specifications; the number of units per sample to collect for each drug and basic info.

All technical information to be collected for each sample is complete and accurate.

The PMS-RB plan defines the locations at which samples will be collected, the drugs to be sampled, the minimum units of doses to be collected for each sample, the number of samples to be collected for each drug, and the total number of samples to be collected in the area for which the sampling plan is prepared she has. It also contains detailed instructions for sample collectors.

Based on risk these products may be targeted for PMS surveillance at any time.

The schedule for risk-based of products is made based on risks as:

1. Monitoring new drugs on the market.
2. Drug monitoring based on risks associated with manufacturing complexity, dosage form, stability (e.g., temperature sensitivity), safety/efficacy (e.g., narrow therapeutic window), and demand (e.g., high burden disease), and therapeutic indications (e.g., infectious diseases), or other factors.
3. Quality control of biological at the main entry points. This type of monitoring acts as a first-class intervention, has been shown to prevent the circulation of poor quality biological, and requires close cooperation between regulatory, customs and law enforcement authorities.

4. Coordination with ongoing sampling and testing initiatives, such as: sampling and testing activities conducted by national health programs (e.g., Office of Malaria, Tuberculosis, HIV/AIDS, Office of Family Health).

7. Framework for risk-based post-market surveillance tool

7.1 Selection of biological product

The number of biological authorized to be on the market varies from one country to another. Controlling the quality of all biological registered is extremely difficult and often unfeasible, so applying risk-based approaches to select biological for sampling and testing as part of a post-marketing surveillance program is imperative that is why grouping of biological done according to:

a) Lot-Release (LT) policy
b) Post marketing surveillance (PMS) classification factors:

Factors Considered		Low	Medium	High
Stability Profile	Accepted storage > 2-8	√		
	2-8 only and DF, and PFL and /or		√	
Packaging or formulation	lyophilized with dil	√		
	Liquid		√	
Previous complaints history CC or SF	complaints(CC, supply chain)		√	
	counterfeit SF			√
Lisence Authourization	Specialized use (certain use)	√		
	Emergency use , widespread campaigns		√	
Availability of the medicine (market access)	Shortage	√		
	Available		√	

Risk Matrix for Categorization of selected biological

low-risk 1-6 **moderate-risk 7-9** **high-risk ≥ 10**

According to these factors biological will be classified into: -

Group (1) High-risk products

Group (2) Medium-risk products

Group (3) Low-risk products

7.2 Selection of geographical area for sampling

The governorates will be classified using their geographical regions and based on the following classification factors: Population Size, Border zone / ports, Supply chain, transportation from the central stores to regions, Storage performance and history of cold chain complaints and History of Counterfeit and sub-standard

		Low	Medium	High
Population size	> 6 millions			√
	3 - 6 millions		√	
	< 3 million	√		
Border zone / (air) ports	If present			√
Poor supply / transportation from the central stores (regions)	G. Cairo & Alex.			√
	Delta & Canal regions		√	
	Upper Egypt Region			√
Poor storage condition / Cold Chain (CC) complaints	<6 CC complaints / year	√		
	6-12 CC complaints / year		√	
	> 12 CC complaints / year			√
Presence of SF medicine	Counterfait history complaints			√

- Risk Matrix for Categorization of geographical area for sampling

Low-risk < 6 **moderate-risk 6-10** **high-risk > 10**

Follow-up of the cold chain for the stores of biological and vaccines products in all the places they pass through in all the governorates will be done.

According to these factors geographical area will be classified into: -

Group I: High-risk governorates:

Withdrawals are made from these governorates for products in groups (1, 2 & 3) at a rate of three times every quarter.

Group II: Medium-risk governorates:

Withdrawals are made from these governorates for products in groups (1, 2 & 3) at a rate of twice every quarter

Group III: Low-risk governorates:

Withdrawals are made from these governorates for products in groups (1, 2 & 3) at a rate of once every quarter

Biological group	High-risk governorates	medium-risk governorates	low-risk governorates
High-risk	3 times/quarter	2 times/quarter	1 times/quarter
Medium-risk	3 times/quarter	2 times/quarter	1 times/quarter
Low-risk	3 times/quarter	2 times/quarter	1 times/quarter

7.3 Collection Site

- Collection of samples from ports of entry are excluded since verification of consignments is done by inspectors from EDA, & consignments are released under restricted release conditions to warehouses of distributers, wholesalers,…etc. and is checked by inspectors from EDA for final release or sampling for testing.
- Withdrawals are made from main outlets ***(Level 1)*** like the stores of distribution companies and/or private stores and warehouses (medical stores - drug stores - regional stores of the governorate, Intermediate vaccine stores and medical districts) and secondary outlet ***(Level 2)*** like local pharmacies and pharmacies inside general and specialized hospitals and health care units.

7.4 Number of collected samples

Required quantity of samples which needed for issuing complete report should be collected with reference to the NCL guidance document on quantity of samples required for analysis.

Samples are drawn according to the size of the bottle/vials from the same batch number to be as follows:

Samples with volume less than 1 ml: five samples
Samples with volume between 1- 4 ml: three samples
Samples with volume 5 ml and more: 2 samples

7.5 Frequency of sampling

According to the previous factors a PMS risk-based sampling matrix will be done like:

Group (1) High-risk products:

- These products are withdrawn and analyzed three times annually, twice from the main outlets (distribution companies, stores and warehouses) and once from a secondary outlet (one of the pharmaceutical institutions).
- At least one sample Withdrawn from one of the ports of a governorate with high and/or medium risks, with follow-up of the cold chain and storage in all governorates.
- Conducting major tests (Relevant test)

Group (2) Medium-risk products:

- These products are withdrawn and analyzed twice a year, once from one of the main outlets (distribution companies, stores and warehouses) and once from a secondary outlet (one of the pharmaceutical institutions).
- At least one sample Withdrawn from one of the ports of a governorate with high and/or medium risks, with follow-up of the cold chain and storage in all governorates.
- Conducting major tests (Relevant test)

Group (3) Low-risk products:

- These products are withdrawn and analyzed twice a year, twice from a secondary outlet (a pharmacy institution).
- Samples will be withdrawn twice during the year from any governorate, with the follow-up of the cold chain and storage in all governorates
- conducting the main tests (Relevant test)

Product Risk	Frequency of sampling/year	Site of sampling	Region of sampling	Testing
High	3	2 from level 1 1 from level 2	At least 1 from high or medium risk region	Relevant
Medium	2	1 from level 1 1 from level 2	At least 1 from high or medium risk region	Relevant
Low	2	2 from level 2	any	Relevant

[*Risk based matrix for sampling*]

8. Implementation of Plan

After developing the PMS risk-based plan which provide all technical information about the tests to be used, product specifications, the number of units per sample to collect for each drug and basic information regarding the stability of the drugs and proper handling during sampling and the notification of all concerned parties of the risk-based plan.

The drug authority inspectors will implement the PMS risk-based (PMS-RB) process and start sampling after making an inspection report for the pharmaceutical institution, from which the risk-based will be made, indicating the availability of good storage requirements for the institution, as well as describing the storage conditions of the withdrawn product, in addition to the necessity and quality of documents indicating a source of supply of the product indicating the supplier, batch number and date of supply.

Visual check is done for outer packaging and inner leaflet of the product and to mention any notes in case there are any changes while matching the drawn sample to an original sample.

Visual examination of the drug is carried out to monitor the presence of impurities, the appearance of mold, or a change in the physical properties of the product and take notes, if there are any.

9. Sampling collection

The number of samples corresponding to the risk-based plan is drawn randomly, in preparation for sending them for analysis

The sampling form shall be filled out showing all the technical information (including the location of collection, the number of samples collected, the name of the sample and any note at the time of collection) that will be collected for each complete and accurate sample, and it shall be signed by the authority's inspectors as well as the director of the pharmaceutical establishment

10. Product Information Review and confirmatory testing

- Results of the product information review and confirmatory testing will be completed.

- Testing results will be shared with Market control & surveillance unit in EDA for sharing information with relevant stakeholders and taking further regulatory actions.

11.Analyze, Communicate & Act:

Regular meetings are held with all interested parties that will be in direct or indirect contact and will be affected by the risk-based plan by mean or another to clarify all the vague points for instance refunding the pharmaceutical institutions for the withdrawn products and the response in case of non-conform sample.

Depending on the data presented to the NCL and the potential public health importance of the findings, the authority may take a variety of actions, including but not limited to further testing of samples and requesting additional information or clarification from market authorization holders, or other appropriate regulatory action such as recall

12. Conclusion:

Data from sampling and testing activities within post marketing surveillance programs can be used to strengthen the programs themselves and should be used to continuously shape, refine, and improve future activities and national post-marketing surveillance priorities.

13. References:

1. WHO Technical report series 996 Annex 7, Guidelines on the conduct of surveys of the quality of medicines, 2016.

2. Guidance for implementation Risk-Based post marketing quality surveillance in low and middle income counties. PQM. Promoting the Quality of Medicines USAID and USP, February 2018.